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(54) Title: STIMULATION OF AN ANTITUMOR T-CELL RESPONSE USING ANTI-IDIOTYPIC ANTIBODIES

(57) Abstract

Anti-idiotypic antibodies containing internal images which mimic tumor associated antigens are useful as vaccines to stimulate a T-cell immune response in a tumor bearing subject or in a subject at risk for malignancy. The antibodies are administered and the T-cell response of the subject is monitored in order to assess the efficacy of the protocols and/or the antibodies are administered in combination with an adjuvant known to enhance T-cell responses.

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STIMULATION OF AN ANTITUMOR T-CELL RESPONSE USING ANTI-IDIOTYPIC ANTIBODIES

Technical Field

The invention is related to the field of interfering with the progression of malignancies or other tumors. More specifically, the invention concerns use of anti-idiotypic antibodies to produce an antitumor cytotoxic and/or helper T-cell response.

Background Art

The use of anti-idiotypic antibodies which represent an internal image of a tumor antigen to raise antibodies when administered to tumor-bearing subjects is known. U.S. Patent 5,053,224, issued 1 October 1991, describes the preparation of both polyclonal and monoclonal anti-idiotypic antibodies that recognize the peritope of an antitumor antibody. The issued patent further describes the use of these anti-idiotypic antibodies to stimulate the production of anti-anti-idiotypic antibodies in tumor patients. The anti-idiotypic antibodies are administered, it is stated, in ways generally known to introduce the antibody into the circulatory system in sufficient amounts to stimulate the production of anti-anti-idiotype antibodies.

Several articles in the open literature describe similar work also conducted by the patentees in the above-referenced patent. For example, Herlyn, D. et al., Proc Natl Acad Sci USA (1987) 84:8055-8059, describe the treatment of 30 patients with alum-precipitated polyclonal goat anti-idiotypic antibodies to a tumor marker or "tumor associated antigen" (TAA) and the development in these patients of anti-anti-idiotypic

antibodies. Herlyn, D. et al., Eur J Immunol (1987) 17:1649-1652, describe the use of these goat polyclonal antisera to raise anti-anti-idiotypic antibodies in rabbits. This work was further summarized by Herlyn, D. et al. in Intern Rev Immunol (1989) 4:347-357.

Similar experiments using the murine anti-idiotypic monoclonal antibody MF11-30, which bears the internal image of the human high molecular weight melanoma-associated antigen showed that anti-anti-idiotypic antibodies were formed in melanoma patients administered this Mab (Mittelman, A. et al., J Clin Invest (1990) 86:2136-2144). These workers also showed a remission in one patient who received the anti-id.

Further, Chen, J-J et al., J Immunol (1989) 143:1053-1057, showed that administration of murine anti-idiotypic antibodies to tumor-bearing mice increased survival time. A combination of this therapy with cyclophosphamide treatment produced enhanced survival in these mice.

A paper by Kennedy, R.C. et al., J Clin Invest (1987) 80:1217-1224, cites a number of other references wherein the injection of mice with an anti-id preparation that appears to mimic the tumor antigen structure is said to induce anti-tumor immunity in tumor-bearing animals or humans (Nepom, G.T. et al., Proc Natl Acad Sci USA (1984) 81:2864-2867; Gorczynski, R.M. et al., Cancer Res (1984) 44:3291-3298; Dunn, P.L. et al., Immunol (1987) 60:181-186). The paper also cites an additional report by Herlyn, D.A. et al., Science (1986) 232:100-104. A number of other studies are also cited in this article with respect to the general effect on patient recovery in response to administration of anti-idiotypic antibodies. The paper continues to speculate on the role of "regulatory idiotypes" in the induction of tumor immunity; regulatory idiotypes appear to be independent

of the peritope regions of the idiotypic antibodies.

Subsequent to the invention herein, an article was published by Robins, R.A. et al., Cancer Res (1991) 51:5425-5429, describing the production of interleukin-2 in colorectal cancer patients that have been immunized with human monoclonal anti-idiotypic antibody. The patients were administered a human monoclonal antibody that reacts immunospecifically with the binding site of a murine monoclonal antibody which in turn binds to a tumor marker. An aluminum hydroxide precipitate of the anti-idiotypic Mab resulted in the production of anti-anti-idiotypes and enhancement of IL-2 levels in plasma. Additional evidence of cellular response to immunization was obtained in blastogenesis assays. However, skin test responses were not observed. As the skin test was designed to show T-cell response, and as no evidence from this assay of T-cell response was obtained, it cannot be concluded that the elevation of IL-2 levels necessarily reflects T-cell activation.

The present invention concerns the use of anti-idiotypic antibodies to induce an antitumor T-cell response in tumor-bearing subjects.

Disclosure of the Invention

The invention results from the recognition that the essential elements of the ability of anti-idiotypic antibodies to mediate antitumor activity in a subject resides in their ability to cause the subject to mount a T-cell response to a tumor associated antigen (TAA). Thus, the progress of a method to induce an antitumor response using an anti-idiotypic antibody which mimics a TAA involves monitoring the T-cell response of the subject and in aiding the subject in mounting such a response by supplying the anti-id in conjunction with at least one adjuvant which stimulates T-cell response.

Thus, in one aspect, the invention is directed to a method to induce and monitor an antitumor T-cell mediated response in a tumor-bearing subject which method comprises administering an anti-idiotypic antibody to the subject. The anti-idiotypic antibody has an internal image that mimics a tumor associated antigen characteristic of the tumor that afflicts the subject. The subject is monitored to ensure that a T-cell response is obtained and the protocol can then be adjusted accordingly.

In another aspect, the invention is directed to a composition which is useful to elicit an antitumor T-cell-mediated response. The composition contains, in addition to at least one anti-idiotypic antibody with an internal image that mimics the relevant tumor associated antigen, an adjuvant which encourages a T-cell response in the subject. In still another aspect, the invention is directed to a method of treatment using these compositions.

Modes of Carrying Out the Invention

The invention takes advantage of the ability of anti-idiotypic antibodies with appropriate internal images to cause a subject to which they are administered to mount a T-cell response to a tumor associated antigen. As used herein, "anti-idiotypic antibody" is used in its art-recognized sense. When a subject is immunized with an antigen, antibodies capable of binding that antigen specifically do so because of a region of the antibody which is an "idiotype" unique to antibodies raised with regard to the stimulating antigen. Thus, the conventional antibody-antigen specific immunoreactivity, which is used to advantage, for example, in the conduct of immunoassays, relies on the ability of "idiotypic" antibodies to bind antigen.

The idiotypic region of the antibody is not perfectly coextensive with the "paratope", i.e., that region which is most complementary to the epitope residing on the antigen. However, the same general regions of the antibody are involved.

If the idiotypic antibodies raised in response to the antigen immunization are themselves treated as antigens, either because they are deliberately administered, or by virtue of their generation *in situ* in the first immunization, a secondary population of antibodies called "anti-idiotypic" antibodies is raised. These are antibodies which have unique regions by virtue of their ability to bind the idiotypic antibodies. A certain portion of these anti-idiotypic antibodies will mimic the structure of the epitope presented by the original antigen and to which the anti-ids bind. This subset of the anti-idiotypic population thus in effect behaves in a manner similar to the original antigen.

The anti-idiotypic antibodies of the invention are those which bear such an internal image--i.e., they mimic a tumor associated antigen which characterizes the tumor against which a T-cell response is to be mounted.

In general, the idiotypic or anti-idiotypic regions of antibodies are located in the immunoreactive portions of the antibody molecule. Thus, as used herein, "antibodies", unless otherwise specified or evident from the context, are intended to include such immunologically reactive fragments, such as, most commonly, Fab, Fab', and $F(ab')_2$ fragments.

Ways to prepare both monoclonal and polyclonal anti-idiotypic antibodies which mimic tumor associated antigens is described in detail in U.S. Patent 5,053,224, the disclosure of which is incorporated herein by reference. Briefly, polyclonal anti-idiotypic antibodies may be produced by immunizing animals with monoclonal

idiotypic antibodies and screening for antisera which react with idiotypic antibodies to tumor associated antigens. Preferably, a competition assay between the TAA and the antisera is employed; the anti-ids which mimic the antigen are successful competitors. The antisera can be purified by sequential adsorption with immobilized antibody of the same isotype as the monoclonal idiotypic antibody but a different idiotype in order to remove antiisotypic antibodies from the antisera and then with the immobilized monoclonal idiotypic antibody to remove the remaining anti-ids. The purified sera can then be again tested for their ability to bind idiotypic antibodies in competition with TAA.

Monoclonal antibody preparations from such animals may also be prepared using standard techniques of immortalizing the antibody secreting cells of the animal and screening the cultures with idiotypic antibodies in competition with TAA. Human or murine monoclonals are preferred; polyclonal preparations in a variety of mammalian systems may also be used.

The anti-idiotypic antibodies of the invention, and the immunologically reactive fragments thereof may also be produced using recombinant techniques provided the relevant portions are sequenced so as to permit the construction of suitable variable regions. Recombinant production of such antibodies or fragments permits the use of chimeric antibodies as well as those natively produced.

Administration and Use

In the method of the invention, the anti-idiotypic antibodies are administered for both prevention and treatment of malignancy including solid tumors, for example, tumors located in the lung, colon, rectum, stomach, breast, prostate, pancreas, uterus, ovary,

urinary tract, skin, oral cavity, liver, bone, brain, endocrine glands, connective tissue, esophagus, eye and melanoma as well as malignancies of the blood and lymph nodes such as leukemia, lymphoma, and multiple myeloma.

The anti-idiotypic antibodies of the invention are administered as antitumor vaccines to subjects at risk for the development of malignancy or showing a diagnosis thereof. The compositions are formulated for parenteral administration or for aerosol administration using formulations appropriate to the administration route, such as those described in Remington's Pharmaceutical Sciences, latest edition, Mack Publishing Company, Easton, PA.

Suitable routes for parenteral administration include injection, including intraperitoneal, intramuscular, intravenous, and subcutaneous injection. For formulation for injection, the antibodies are generally formulated in a suitable liquid such as Hank's solution or Ringer's solution, along with suitable excipients providing buffering, stabilizing, and other desirable characteristics, as well as additional components if desired as further described below. Alternative routes for parenteral administration include transmucosal and transdermal administration, generally involving excipients which enhance permeation such as bile salts, fusidic acids, detergents, and the like. For aerosol administration, which is one form of transmucosal administration, additional components for stabilizing the aerosol may also be included.

In addition to administration in an appropriate isotonic vehicle for injection, liposomes are desirably used as a carrier to direct the product to the immune system as disclosed in copending application 07/800,474, the disclosure of which is incorporated herein by

reference.

In general, the dosage range for the antibodies of the invention is of the order of 0.01 μg-100 mg per dose, preferably 0.1 μg-10 mg per dose, and more preferably 1 mg-5 mg per dose. Suitable volumes for parenteral administration are about 0.1-5 ml.

The antibodies of the invention are administered, generally, in multiple doses typically once per week for one or two months and with decreasing frequency thereafter for a period extending about one year. Following the initial one-year course of vaccination, booster inoculations may be given every two months to five years. Alternate protocols may be appropriate in individual instances.

In addition, it may be advantageous to substitute, for the first single administration of the initial one-year protocol, rather than the anti-ids of the invention, a recombinant form of the antigen (whose image is borne by the anti-ids) wherein the antigen gene is administered in a viral expression vector such as a vaccinia virus. Such viral vectors are described, for example, by Hruby, D.E., Vet Parasitol (1988) 29:281-282, and by Iiu, S.-I., in "AIDS Research Reviews," Dekker, Inc., (1991) 1:403-416. The viral vectors may be administered in the traditional manner via a skin scratch, or may be included in a liposome injectable as described above.

While the antibodies of the invention may be administered alone, it is a further feature of the invention that these antibodies are administered along with adjuvants which enhance the cellular immune response to the anti-idiotypic antibody. Such adjuvants include, but are not limited to, Freund's Complete Adjuvant, Bacillus Calmette-Guerin (BCG) and other bacteria, adjuvant polysaccharides such as glucan, acemannan, lentinan; saponins, detoxified endotoxin (DETOX), muramyl

tripeptide, muramyl dipeptide and their derivatives, SAF1, lymphokines and cytokines such as IL-2 and interferon as well as colony stimulating factors such as GM-CSF, lipid A, monophosphoryl lipid A, alum or immune stimulating complexes in general (ISCOMS).

Monitoring the Cellular Immune Response

As the anti-idiotypic antibodies of the invention effect the regression of tumors through a chiefly cellular mechanism, the efficacy of the treatment is monitored using measurements of the cellular immune response. Such monitoring permits adjustment of the protocol to enhance the effectiveness of the drugs. In general, the assessment of T-cell response is conducted, first, immediately before the start of the protocol in order to establish a baseline; and then determinations are made weekly, biweekly or monthly after the start of the protocol for about 6 months and at decreased frequency thereafter. Of course, any convenient timing strategy appropriate to the individual case may be used.

A number of methods for monitoring cellular immune response are available. The most useful of these is the skin test reaction which is a classic measure of cellular activity which is described in detail as applied to patient testing by Spitler, L.E., in "Manual of Clinical Immunology", Rose, N.R. et al., eds., Am Soc Microbiol, Washington, D.C. (1976) pgs. 53-63. Briefly, a test antigen is injected intradermally in about 0.1 ml saline or other isotonic solvent and the reaction is read 24-48 hours after injection. The reaction consists of the development of erythema and induration at the test site with associated characteristic histopathological changes. These changes may be demonstrated by biopsy.

For human subjects immunized with murine anti-

idiotypic antibodies, the immunizing antibody cannot be used as the test antigen since positive response would simply reflect reactivity to the murine component of the immunogen. Tumor cells or their extracts or pure tumor antigens should be used as the test antigen. Controls include injection of the solvent alone to rule out nonspecific dermal reactivity or injection of unrelated tumor cells or antigen to demonstrate specificity.

Another test for cellular response comprises lymphocyte stimulation. In this approach, the response of the patient's lymphocytes to the test antigens and suitable controls is measured in vitro. This response, a blastogenesis, is accompanied by increased DNA synthesis which can be measured by adding labeled DNA precursors such as thymidine or uridine as described by Spitler, L.E. et al. in "Methods of Cancer Research", Busch, H. ed., Academic Press, NY (1973) 8:59-106.

In still another approach, the toxicity of the subject's peripheral blood or lymph node lymphocytes to tumor cells can be measured *ex vivo* in a standard radioactive chromium release assay as described by Yanelli, J.R. et al., J Immunol (1985) 135:900-905. Purified lymphocytes from the test subject are cultured with ^{51}Cr tagged tumor cells; varying numbers of effector cells are added to the tumor cells in microtiter plates and the plates are incubated for sufficient time to release label into the supernatant. The supernatants are then removed and counted.

In addition, a limiting dilution assay of cytolytic lymphocyte precursors can be conducted. This method, which is more sensitive than the lymphocyte toxicity method of the previous paragraph involves restimulation of lymphocytes in the peripheral blood by tumor cells or antigen *in vitro*. This causes proliferation of the target cell as described by Vose, B.M. et al., Int J

Cancer (1982) 30:135-142 and by Mitchell, M.S. et al., Cancer Res (1988) 48:5883-5893. The method measures both precursors of cytolytic lymphocytes and mature effector cells. Purified peripheral blood lymphocytes from the test subject are cultured with irradiated tumor cells, using appropriate controls. To test for cytotoxicity, the tumor cells are labeled with radioactive chromium and added to the cultured lymphocyte/tumor cell mixture. Results are assessed by determining the radioactive chromium release after an additional period of culture. The specificity of the cytolytic reaction can be determined by using different target cell lines such as irrelevant tumors of the same and different histological types as that represented by the immunizing antibody.

Finally, interleukin-2 in plasma can be used as an index *in vivo* of T-cell activation. Plasma levels of IL-2 can be measured conveniently using standard ELISA assays, for example. One such assay is described by Robins, R.A. et al., Cancer Res (1991) 51:5425-5429.

The foregoing methods are convenient measures of cellular responses to the administration of the anti-idiotypic antibodies of the invention. Performance of these monitoring methods is important to assess the efficacy of the therapy and to alter the immunization protocol if needed. Ultimately, action on the tumor directly can be demonstrated by tumor biopsies stained with hematoxylin and/or eosin for standard histopathologic examination to detect inflammation and by assessing the level of tumor regression *in vivo*.

Claims

1. A method to evaluate the ability of an antibody to elicit an antitumor cytotoxic T-cell mediated response in a tumor-bearing human patient which method comprises administering to said patient a monoclonal antiidiotypic antibody having an internal image which mimics an epitope of a tumor associated antigen (TAA) for said tumor to evoke an antitumor cytotoxic T-cell mediated response; and

monitoring said cytotoxic T-cell response to evaluate the efficacy of said antibody in inducing said cytotoxic T-cell response as a correlate of antitumor efficacy.

2. The method of claim 1 wherein said monitoring comprises conducting an assay selected from the group consisting of

assessing the cytotoxicity of the patient's peripheral blood or lymph node lymphocytes to tumor cells, and

conducting a limiting dilution assay of cytolytic lymphocyte precursors.

3. The method of claim 1 or 2 wherein said anti-idiotypic antibody is administered as an Fab, Fab' or $F(ab')_2$ fragment.

4. The method of any of claims 1-3 wherein said administering of said antiidiotypic antibody is preceded by administering the gene encoding said TAA in a viral expression vector capable of effecting the production of said TAA *in situ* in said patient.

5. The method of any of claims 1-4 which further includes administering at least one adjuvant capable of mediating the stimulation of a cytotoxic T-cell response by an immunogen, said combination effective to evoke said cytotoxic T-cell response.

6. The method of claim 5 wherein said adjuvant is selected from the group consisting of Freund's Complete Adjuvant, *Bacillus Calmette-Guerin* (BCG) adjuvant polysaccharides, saponins, detoxified endotoxin, muramyl tripeptide, muramyl dipeptide, SAF1, lymphokines, cytokines, alum, lipid A, monophosphoryl lipid A, and immune-stimulating complexes (ISCOMS).

7. A pharmaceutical composition useful for eliciting an antitumor cytotoxic T-cell mediated response in a tumor-bearing human patient which composition comprises at least one anti-idiotypic monoclonal antibody having an internal image which mimics an epitope of a tumor associated antigen (TAA) for said tumor.

8. The composition of claim 7 which further contains at least one adjuvant capable of mediating the stimulation of a cytotoxic T-cell response by an immunogen.

9. The composition of claim 8 wherein said adjuvant is selected from the group consisting of Freund's Complete Adjuvant, *Bacillus Calmette-Guerin (BCG)*, adjuvant polysaccharides, saponins, detoxified endotoxin, muramyl tripeptide, muramyl dipeptide, SAF1, alum, lipid A, monophosphoryl lipid A, lymphokines, cytokines, and immune-stimulating complexes (ISCOMS).

10. The composition of any of claims 7-9 which further contains a carrier that is taken up by the reticuloendothelial system.

11. The composition of claim 10 whererin said carrier comprises liposomes.

12. The composition of any of claims 7-11 wherein said anti-idiotypic antibody of said composition is a Fab, Fab' or $F(ab')_2$ fragment.

13. A method to evaluate an antitumor response to an antibody in a tumor-bearing human patient which method comprises administering to said patient a monoclonal antiidiotypic antibody having an internal image which mimics an epitope of a tumor associated antigen (TAA) for said tumor to evoke said antitumor response; and

monitoring said antitumor T-cell response by assessing the inflammatory response of a tumor biopsy from said subject, wherein enhanced inflammation denotes an antitumor response.

14. The method of claim 13 wherein said antiidiotypic antibody is administered as an Fab, Fab' or $F(ab')_2$ fragment, and/or

wherein said administering of said antiidiotypic antibody is preceded by administering the gene encoding said TAA in a viral expression vector capable of effecting the production of said TAA *in situ* in said patient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/08163

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 39/395, 39/44; G01N 33/53, 33/536
US CL :424/85.8, 88; 435/69.1, 320.1; 530/387.1, 387.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/85.8, 88; 435/69.1, 320.1; 530/387.1, 387.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, DIALOG, BIOSIS, EMBASE, MEDLINE, WPI
search terms: sptiler, anti-idiotyp?, vaccine, tumor, cancer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. Immunol., Volume 142, No. 3, issued 01 February 1989, Y. Saeki et al., "Characterization of Regulatory Idiotope-Specific T Cell Clones to a Monoclonal Anti-Idiotypic Antibody Mimicking a Tumor-Associated Antigen (TAA)", pages 1046-1052, see entire document.	1-14
Y	J. Clin. Invest., Volume 80, issued November 1987, R.C.Kennedy et al., "Possible Role of Anti-Idiotypic Antibodies in the Induction of Tumor Immunity", pages 1217-1224, see entire document.	1-14

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Veterinary Parasitology, Volume 29, issued November 1988, D.E.Hruby, "Present and Future Applications of Vaccinia Virus as a Vector", pages 281-292, see entire document.	1-14
Y	Ann. Surg., Volume 202, No. 1, issued July 1985, W.H. Cole et al., "Need for Immunologic Stimulators During Immunosuppression Produced by Major Cancer Surgery", pages 9-20, see entire document.	1-14
Y	Proc. Natl. Acad. Sci., Volume 81, issued January 1984, H. Koprowski et al., "Human Anti-Idiotype Antibodies in Cancer Patients: Is the Modulation of the Immune Response Beneficial for the Patient?", pages 216-219, see entire document.	1-14
Y	J. Immunol., Volume 137, No. 5, issued 01 September 1986, S. Raychaudhuri et al., "Tumor-Specific Idiotype Vaccines", pages 1743-1749, see entire document.	1-14
Y	Science, Volume 232, issued 04 April 1986, D. Herlyn et al., "Anti-Idiotypic Antibodies Bear the Internal Image of a Human Tumor Antigen", pages 100-102, see entire document.	1-14
Y	E. Harlow et al., ANTIBODIES A LABORATORY MANUAL, published 1988 by Cold Spring Harbor Laboratory, see pages 96-97.	1-14